THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION: Barros et al.	§	
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Serial No.: 10/528,500	§	**Group Art Unit: 1655**
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Filed: March 18, 2005	§	**Examiner: Tate, Christopher R.**
	§	
For: Gel Composition Comprising 4-Nerolidylcatechol and Uses Thereof	§	
	§	

Mail Stop Appeals
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

ATTENTION: Board of Patent Appeals
and Interferences

APPELLANT'S REPLY BRIEF (37 C.F.R. § 41.41)

In the Examiner's Answer mailed November 20, 2009, the Examiner made a statement that Applicants wish to address. Accordingly, this reply brief is being filed, pursuant to 37 C.F.R. § 41.41.

The Examiner asserts that the subject-matter of claims 24, 27 and 28 is not supported in the specification. However, Applicants assert that a gel composition for the treatment and/or prevention of photodamage to skin, cutaneous ageing and/or skin cancer, on the basis of *Photomorphe umbellate* extract comprising a standardized extract of *Photomorphe umbellate* which contains a range from 0.005 to 20.0% of 4-nerolidylcatechol in the composition, as claimed in claim 24, is fully supported by

specification of the present application (paragraph 30). Likewise, the claimed gel composition, "comprising carboxymethylcellulose 0.01-10. %; propyleneglycol 0.001-50.0%; methylparaben 0.001-3.0% and *Pothomorphe umbellata* standardized extract, so that the formulation comprises from 4-nerolidylcatechol 0.005 to 20.0%" claimed in claims 24 and 28 are also fully supported by the specification.

The preparation of the composition itself is not specifically described in the specification, however it is mentioned that the composition of this invention can be made through any know methods in the pharmacy art. Therefore, Applicants are claiming only a gel composition and a method of treating comprising topically administration with said gel composition, and not the process of preparation of gel composition. Additionally, the specification mentions that a possible source for 4-nerolidylcatechol is a *Pothomorphe umbellate* rot extract. Although it is not specifically mentioned in the specification, someone skilled in the art would know that 4-nerolidylcatechol could be obtained by any other means (other plants extracts, organic synthesis, etc).

Moreover, examples 1 and 2 of the present application specifically demonstrate the effect of the topical application of a gel containing 0.1% of 4-nerolidylcatechol. Example 1 teaches that a topical application of a gel containing 0.1% of 4-nerolidylcatechol preserve the levels of tocopherol in the skin of irradiated mice, thus protecting it against degradation from UV radiation. Example 2 teaches that a topical application of a gem composition containing 4-nerolidylcatechol in the concentration of 0.1% reduced photoaging in the skin of UV irradiated mice. These examples fully support to claims 27 and 28.

The Examiner also asserts that the subject-matter of claims 24, 27 and 28 obvious in view of the cited references. Applicants respectfully disagree. First of all, it would not be obvious as to what specific combination of common skin gel components to use in such gel composition comprising 4-nerolidylcatechol. Secondly, it would not surely be obvious as to what quantities of each of the components should be used in said gel composition.

Applicants emphasize again that in page 7, line 16 of the specification, it is stated that although the antioxidant activity of *Pariparoba* was known, it is not obvious to imagine, which specific gel formulation serves as a vehicle for this drug in order to obtain a therapeutically effective gel composition. Furthermore, there are not specific studies about the performance of active principle of this plant in the oxidative stress caused by ultraviolet radiation. Figure 3 shows the effectiveness of the proposed vehicle, showing that 4-NC is present on (into) the skin. In the present application, it was demonstrated for the first time the activity ***in vivo*** of the extract in mice chronically exposed to ultraviolet radiation.

Barros et al is considered the closest prior art, since it relates to a purified fraction of the ethanolic extract of *Pothomorphe umbellata*, containing 4-nerolidylcatechol that has antioxidant activity. The technical difference between the composition of *Barros et al* and the present invention is the use of a gel composition. The technical effect conferred by this difference is that the gel composition of present application is suitable for topical application on the skin and thus favors the absorption of the active principle by the skin.

The objective technical problem faced by Applicants was to treat ***in vivo*** and/or prevent ***in vivo*** photodomage, both to skin, cutaneous aging and/or skin cancer. This problem is solved by providing a gel composition comprising i) as an active principle, a *Pothomorphe umbellata* standardized extract, so that the formulation comprises from 4-nerolidylcatechol 0.005 to 20.0%, and ii) carboxymethylcellulose (0.01-10.0%), propyleneglycol (0.001-50. 0%) and methylparaben (0.001-3.0%).

Although it is common sense that antioxidants are especially helpful for preventing or treating skin aging, it is also well known that a molecule cannot be considered an antioxidant by its intrinsic or *in vitro* behaviour, said antioxidant activity being strictly related to the environment in which it is. For example, epigallocathechin is a well known "antioxidant", which under certain conditions (e.g. cell cultures) can act as a pro-oxidant. *In vitro* cytotoxicity of epigallocatechin gallate and tea extracts to cancerous and normal cells from the human oral cavity. The same applies to vitamin C in the presence of high amounts of iron. The most accepted definition of the term antioxidant is any substance that delays, prevents or removes oxidative damage to a target molecule.

Actually, the *Pothomorphe umbellata* roots extract showed an antioxidant potential significantly larger than the one of this isolated compound, suggesting the presence of additional compounds having antioxidant activity are present in *Pothomorphe unmbellata* extract. The specific combination of the components of the claimed gel composition enables the active principle to permeate the skin and thus be able to act as an antioxidant under these conditions. This activity depends on the surroundings of said substance and can neither be inferred nor predicted with precision based only on *in vitro*

experiments. Hence, even in cases where a particular compound behaves as a good antioxidant under in vitro experimental conditions (such as those presented in *Barros et al*), this absolutely does not mean that it will act the same when applied on the skin.

Barros et al provides no teaching as to how crude extracts of different parts of *Pothomorphe umbellata* or isolated 4-nerolidylcatechol compound would act *in vivo*. *Barros et al* only refers to *in vitro* experiments [see abstract, lines 4-5]. Additionally, there is no indication in *Barros et al* whether *Pothomorphe umbellata* extracts or isolated 4-nerolidylcatechol exhibit photostability properties.

The present invention has shown that it is the specific combination of the components of the claimed gel composition that grants its therapeutic properties. It is well known in the art that a given antioxidant must permeate active compound must permeate the *stratum corneum* and reach the viable skin to exert its antioxidant activity. This permeation depends not only on the structure of the antioxidant compound itself but also on the specific formulation used and the interaction between the compound itself and the formulation used with the skin.

In vivo efficacy of the present invention relates to percutaneous absorption which involves the dissolution of the compound of the invention in a vehicle, diffusion of the solubilized compound from the vehicle to the surface of the skin, and the penetration of said compound through the layers of the skin, mainly the *stratum corneum*. As discussed above, this penetration may be improved and is strongly dependent on the selection of the appropriate vehicle that, once again, is decided in a case to case basis and cannot be predicted or inferred. Many factors may influence the extent of the percutaneous absorption. Partitioning of the compound between the vehicle and the *stratum corneum*

leads to a concentration gradient that is developed across the skin, which is influenced by compound/vehicle/skin interactions.

The primary requirement for topical therapy is that a compound incorporated into a vehicle actually reaches the skin surface at an adequate rate and in sufficient amounts and this cannot be achieved without duly experiments performed by the inventors of the present invention. The flux is indeed proportional to the gradient of thermodynamic activity, rather than to the concentration of the compound. The activity of even slightly different formulations changes depending on said differences and the release of a substance from the vehicle will be favored by selecting vehicles with low affinity for the penetrating molecule, again in a case to case basis.

The topical skin composition taught by *Uchiyama et al.* was only tested *in vitro* and it is therefore impossible to predict from the reference what specific gel composition comprising an extract of *Pothomorphe umbellata* and/or 4-nerolidylcatechol would exhibit the desired permeability essential for therapeutic purposes. Example 1 of the present application demonstrates that the claimed composition has indeed the ability to deliver 4-nerolidylcatechol into the skin (FIG. 3) and can therefore be used topically for therapeutic purposes.

Additionally, in order to exhibit photoprotective properties, a given antioxidant must be photostable after UV exposure. Previous studies of *Pothomorphe umbellata* extracts have not employed UV radiation and it was thus not obvious at time of the claimed invention as to which specific formulation containing an extract of *Pothomorphe umbellata* and/or 4-nerolidylcatechol would be photostable. The results shown in Example 2 of the present application clearly demonstrate that the claimed composition is

capable of protecting the skin against UV radiation after UV exposure and therefore exhibits the desired photostability properties (FIG. 5). The Examiner fails to understand that the inventive activity of present application is focused on developing of formulation containing extract of the plant and that it contains the 4- nerolidylcatechol so that the final concentration of this compound in the formulation is between 0.005 to 20% to produce a photoprotector effect ***in vivo***.

Ropke et al (2002) mentioned in the summary the use of gel, but the components of the gel were not specified. Furthermore, as explained on page 9 of Applicants' Appeal Brief, Ropke et al (2002) should be not is considered by Examiner as prior art, since that it was published by the own inventors within the grace period of the present application.

However, Ropke et al (2002) does not teach a gel. There are four categories of semi-solid preparations: ointments, creams, gels or paste. Gels are semi-solid system consisting of suspensions of small inorganic particles or large organic molecules interpenetrate by a liquid, as the formulation on the present application, while ointment are preparations for topical application, consisting of single base, which may be dispersed solids or liquids, for example, Diadermine. As known by one of ordinary skill in the art, gel and diadermine compositions are completely different and the incorporation of active ingredient in these compounds results in therapeutics effects completely different.

The Examiner asserts that Wheeler et al. teaches that carboxymethylcellulose, propylene glycol, and methylparaben are well known conventional ingredients within skin therapeutic compositions. However, Applicants assert that the present application is not limited to a simply addition of an antioxidant, but a composition that presents photoprotective activity ***in vivo***, which clearly shows the novelty of the invention. Also

on page 4, paragraph 3, Applicants state that the present application is not based on antioxidant activity but on photoprotective activity (photodamage). It is not possible to say that any substance that presents antioxidant activity is photoprotector. Therefore, it is not obvious to one of ordinary skill in the art to deduce this property. On page 7, line 16 of the specification of the present application, it was mentioned that although the antioxidant activity has been known, the absorption on skin was fundamental to the effect ***in vivo***, which shows "the protection of the skin against ultraviolet radiation".

Uchiyama et al. refers to formulations with antioxidant activity and does not indicate the formulations which are in the form of gel. Barros et al. (1996) and Desmarchelier et al. teach only a composition comprising an antioxidant activity. The Wheeler reference does not show the photoprotective activity of these formulations containing carboxymethylcellulose, propylene glycol, and methylparaben. None of the cited references, including Uchimyama et al., expressly teach providing the skin with therapeutic *Pothomorphe umbellata* extract within a skin gel composition including photoprotective activity.

The therapeutic gel composition of the present application is not merely a matter of common selection and routine optimization which is well within the experience of an expert. The composition of the present application is a formulation in gel containing the extract which allowed the effects claimed in the claim 28. Therefore, it is not obvious that mixing the *Pothomorphe umbellata* extract will induce the photoprotective activity.

All references cited as prior art refers only to the antioxidant activity and Wheeler et al. refers only to compositions for topical use that do not mention the effect claimed by present application, namely, photoprotective activity (photodamage). Together or

separately, the mentioned documents do not compromise the novelty of the present application. None of the references mention the main subject-matter of the present application, which refers to the incorporation of the extract of *Pothomorphe* in a gel formulation, with components specified and with photoprotective activity and other effects as claim 28. In order to obtain these effects, it is necessary permeate the skin, wherein lies the novelty and nonobviousness of the present invention. The Examiner seems to simply ignore these properties that characterize the invention.

Based on the above arguments, it would not have been obvious to imagine an extract of Photomorphe in a gel formulation, with components specified. Furthermore, it would not be possible to foresee that such gel composition with *Photomorphe umbellate* extract has photoprotective activity.

Not all photoprotectors are antioxidants. In most cases, the photoprotector acts as barrier function and has no antioxidant activity. Not all antioxidant have photoprotective activity or have photoprotective activity in equal intensity. One reason for this is that in achieving the effect demonstrated in the present application, the active ingredient must permeate the skin. This effect was only accomplished in the present application (Figure 3 of the specification). The present application was able to dissolve and stabilize the 4-nerodliycathecol, a highly lipophilic molecule, in a totally hydrophilic gel formulation, while at the same time, delivering the active principle into the skin at an adequate rate in sufficient amounts, demonstrating the importance of an appropriate gel composition for an accurate penetration of the drug.

Therefore, given the references above, at the time the claimed invention was filed, it would not have been obvious to one of ordinary skill in the art how exactly to

incorporate 4-nerolidylcatechol (obtained from a *Pothomorphe umbellata* extract or any other source) into a gel composition. That is to say, it would not be obvious as to what specific gel formulation to use in order to obtain a therapeutically effective gel composition. None of the references mentioned above isolated or in combination shows that an extract of *Pothomorphe umbellata* and/or 4-nerolidylcatechol is photostable, thus suggesting their use for protecting the skin against UV radiation after UV exposure. The references also fail to suggest that an extract of *Pothomorphe umbellata* and/or 4-nerolidylcatechol can be used ***in vivo***. Finally, the specific combination of the components of the claimed gel composition that grant its therapeutic properties are not disclosed in any of the cited cited references.

CONCLUSION

In view of the above arguments, Appellant respectfully submits that all the extant claims are allowable over the cited prior art and that the application is in condition for allowance. Accordingly, Appellant respectfully requests the Board of Patent Appeals and Interferences to overturn the rejections set forth in the previous Office Action. No fees are believed to be due, however, the Commissioner is hereby authorized to charge any additional payments that may be due to deposit account 50-0392.

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